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Timing to First Whole Blood Transfusion and Survival Following Severe Hemorrhage in Trauma Patients

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Supplemental content

IMPORTANCE Civilian trauma centers have revived interest in whole-blood (WB) resuscitation for patients with life-threatening bleeding. However, there remains insufficient evidence that the timing of WB transfusion when given as an adjunct to a massive transfusion protocol (MTP) is associated with a difference in patient survival outcome.

OBJECTIVE To evaluate whether earlier timing of first WB transfusion is associated with improved survival at 24 hours and 30 days for adult trauma patients presenting with severe hemorrhage.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study used the American College of Surgeons Trauma Quality Improvement Program databank from January 1, 2019, to December 31, 2020, for adult patients presenting to US and Canadian adult civilian level 1 and 2 trauma centers with systolic blood pressure less than 90 mm Hg, with shock index greater than 1, and requiring MTP who received a WB transfusion within the first 24 hours of emergency department (ED) arrival. Patients with burns, prehospital cardiac arrest, deaths within 1 hour of ED arrival, and interfacility transfers were excluded. Data were analyzed from January 3 to October 2, 2023.

EXPOSURE Patients who received WB as an adjunct to MTP (earlier) compared with patients who had yet to receive WB as part of MTP (later) at any given time point within 24 hours of ED arrival.

MAIN OUTCOMES AND MEASURES Primary outcomes were survival at 24 hours and 30 days.

RESULTS A total of 1394 patients met the inclusion criteria (1155 male [83%]; median age, 39 years [IQR, 25-51 years]). The study cohort included profoundly injured patients (median Injury Severity Score, 27 [IQR, 17-35]). A survival curve demonstrated a difference in survival within 1 hour of ED presentation and WB transfusion. Whole blood transfusion as an adjunct to MTP given earlier compared with later at each time point was associated with improved survival at 24 hours (adjusted hazard ratio, 0.40; 95% CI, 0.22-0.73; $P = .003$). Similarly, the survival benefit of earlier WB transfusion remained present at 30 days (adjusted hazard ratio, 0.32; 95% CI, 0.22-0.45; $P < .001$).

CONCLUSIONS AND RELEVANCE In this cohort study, receipt of a WB transfusion earlier at any time point within the first 24 hours of ED arrival was associated with improved survival in patients presenting with severe hemorrhage. The survival benefit was noted shortly after transfusion. The findings of this study are clinically important as the earlier timing of WB administration may offer a survival advantage in actively hemorrhaging patients requiring MTP.

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Trauma patients presenting to the emergency department (ED) with severe hemorrhage requiring massive transfusion face a substantially increased risk of bleeding-related death within the first 24 hours.[1] Current trauma resuscitative strategies emphasize the significance of a balanced transfusion approach of fractionated blood components to counter trauma-induced coagulopathy (TIC) among these patients, which is associated with up to 50% mortality.[2,3] Despite the advancements in trauma care throughout the years, the impact of hemorrhage as the leading cause of preventable deaths after injury in the US has yet to be overcome.[1]

Recent research has focused on optimizing current hemostatic resuscitation efforts in trauma. A rejuvenated interest in whole blood (WB) to augment current component therapy-based massive transfusion strategies has gained traction within military and civilian trauma settings. Whole-blood resuscitation has been associated with a reduction in 24-hour and 30-day mortality in trauma populations.[4-6] Recent evidence showed that WB transfusion given to a cohort of severely injured patients requiring massive transfusion was associated with a 37% and 47% lowered risk of in-hospital mortality at 24 hours and 30 days, respectively.[7] Most notably, a survival benefit associated with WB among severely injured patients receiving a massive transfusion protocol (MTP) was seen early after transfusion.[5,7]

The underlying mechanism of WB and its associated survival benefit remains unclear. One plausible explanation could be its efficiency as a single product to facilitate an early and timely high-ratio resuscitation inherent to the composition of WB.[8,9] However, the evidence of whether the timing of WB transfusion affects survival in trauma patients with severe hemorrhage is limited. This obscurity within the existing literature may explain why only 24% of American College of Surgeons (ACS)-verified trauma centers use WB[10] and the hesitancy for the ACS Trauma Quality Improvement Program (TQIP) management guidelines to adopt WB as part of MTP. While data have increased that suggest a survival benefit associated with WB use,[2,5,7] understanding when it should be administered may provide further motivation for protocolizing WB as a standard in trauma resuscitative practices.

Therefore, the objective of this study was to analyze survival associated with WB transfusion timing among patients presenting with severe hemorrhage who received WB as an adjunct to MTP in US and Canadian adult civilian trauma centers over a 2-year period. We hypothesized a priori that patients with severe hemorrhage requiring MTP who received WB earlier after ED arrival compared with later would have improved survival at 24 hours and 30 days for any given time point.

Key Points

Question Is the timing of first whole blood transfusion associated with improved early and late survival among adult trauma patients presenting with severe hemorrhage?

Findings In this cohort study of 1394 patients who presented with severe traumatic hemorrhage requiring massive transfusion, less time to first whole blood transfusion was associated with a reduced time to death at 24 hours and 30 days, with a survival benefit seen as early as 1 hour after emergency department arrival.

Meaning These findings suggest the importance of timing to first whole blood transfusion when given as an adjunct to a massive transfusion protocol.

Methods

Study Design

We performed survival and secondary analyses as part of a retrospective cohort study of adult patients treated at level 1 and 2 US and Canadian civilian trauma centers participating in the ACS TQIP between January 1, 2019, and December 31, 2020. The TQIP is a voluntary performance improvement program containing deidentified, risk-adjusted, and validated patient- and hospital-level data collected by trained abstractors. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. The Boston University institutional review board approved the study as an exemption, and informed consent was waived because the abstracted data were retrospectively obtained, deidentified, and publicly accessible.

Study Participants

The study participants were adult (aged ≥18 years) civilian trauma patients presenting with severe hemorrhage who received WB and MTP within the first 24 hours of ED presentation. Severe hemorrhage was defined as systolic blood pressure less than 90 mm Hg, shock index greater than 1, and receipt of MTP. We chose these criteria to define severe hemorrhage, as the combination of a shock index greater than 1 and hypotension on ED arrival has been associated with TIC, increased bleeding-related mortality, and the requisite for MTP.[11-13] The MTP was defined as receiving a balanced ratio of packed red blood cells, plasma, and platelets of 4 or more units transfused within 1 hour from ED presentation up to 4 hours after ED arrival, as has been done in previous studies.[7,14-18] We excluded patients with burns, prehospital cardiac arrest, deaths within 1 hour of ED arrival, and interfacility transfers.

Exposure

All patients received WB as an adjunct to MTP. Patient exposure included those who received WB as an adjunct to MTP (earlier) compared with patients who had yet to receive WB as part of MTP (later) for any given time point within 24 hours after ED arrival (counterfactual exposure). Data on WB use from Trauma Quality Programs Participant Use File 2019 to 2020 level 1 and 2 trauma centers were abstracted using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* procedure codes. Data on the volume of WB transfused within the first 4 hours of hospital arrival had not been collected by TQIP until the beginning of the first quarter of 2020. Therefore, we reported the amount of WB transfused in units rather than volume.

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Outcomes

The primary outcomes measured were survival time at 24 hours and 30 days. Secondary outcomes selected a priori were survival time at 4 hours, major complications, hospital length of stay (LOS), and intensive care unit (ICU) LOS. Finally, we analyzed a subgroup of patients with severe head injuries (head Abbreviated Injury Scale score, ≥3).

Potential Confounders

We included patient baseline demographic, injury, and hospital-level characteristics in each regression model to account for potential confounders (eMethods and eTable 1 in Supplement 1). Race was self-reported or identified by a family member and was included in the analysis because it has been shown to be associated with trauma-related mortality.[19] Categories were Asian, Black, and White.

Statistical Analysis

Data analysis was performed from January 3 to October 2, 2023. Parametric and nonparametric continuous variables were summarized with medians and IQRs. Categorical variables were described as counts and proportions. Independent-sample Mann-Whitney *U* tests and *t* tests were used as appropriate to assess comparisons between groups. Pearson χ^2 tests were used to determine differences among categorical variables; all statistical tests were 2 sided. A 2-tailed $P < .05$ was considered statistically significant. We performed multiple imputations to address data that were missing at random (eMethods in Supplement 1).

We performed a multivariable Royston-Parmar flexible parametric survival hazards regression model to evaluate our primary outcome of 24-hour and 30-day mortality (eMethods in Supplement 1). The model fits a restricted cubic spline to allow model flexibility for the baseline log cumulative hazard on the proportional hazards scale. The advantage of this model is the ability to enable absolute measures of effect—hazard ratio (HR) in this case—to be estimated at all time points and incorporate time-dependent effects.[20-23] Additionally, the flexible parametric survival regression model compensates for the lack of flexibility found in the Cox proportional hazards regression model.[24] Final model selection was based on the lowest Akaike information criterion. Interaction terms and clustering of outcomes were assessed (eMethods in Supplement 1).

We then performed univariate analysis followed by a multivariable logistic regression model to evaluate in-hospital complications (eMethods in Supplement 1). A Cox proportional hazards regression model assessed per-minute increase in time to WB transfusion and survival at 4 hours (eMethods in Supplement 1). Last, for total ICU LOS and hospital LOS, we used a negative binomial regression model (eMethods in Supplement 1). All analyses were conducted with Stata/SE, version 17.0 (StataCorp LLC).

Results

From January 1, 2019, through December 31, 2020, a total of 3500 patients met the criteria for severe hemorrhage. Of those, 2106 (60%) were excluded based on prespecified exclusion criteria. In total, 1394 patients were identified (239 female [17%]; 1155 male [83%]; median age, 39 years [IQR, 25-51 years]; height and weight were missing for 249 patients [18%]). A total of 18 patients (1%) were Asian; 410 (29%), Black; and 787 (56%), White. The study identified 173 ACS-verified trauma centers (110 level 1 [64%] and 63 level 2 [36%] centers) (**Table 1**). The overall 30-day mortality rate was 16%. The median time to first WB transfusion overall was 30 minutes (IQR, 6-31 minutes), and the median time to first product of MTP was 36 minutes (IQR, 9-37 minutes). Patients in the study were profoundly injured, with a median Injury Severity Score of 27 (IQR, 17-35). The median WB units transfused was 2 (IQR, 1-2 units), with 304 patients (22%) receiving more than 2 units of WB within 4 hours. The median hospital LOS was 20 days (IQR, 6-27 days). The median ICU LOS was 11 days (IQR, 3-15 days).

We performed a survival analysis at 24 hours. A survival curve demonstrated a difference in survival within 1 hour of ED presentation and WB transfusion. There was an association between improved survival at 24 hours for earlier WB transfusion compared with later WB transfusion at each time point (adjusted HR, 0.40; 95% CI, 0.22-0.73; $P = .003$) (**Table 2** and **Figure**, A). Similarly, the adjusted survival regression model demonstrated improved survival benefit associated with earlier WB transfusion at every time point at 30 days (adjusted HR, 0.32; 95% CI, 0.22-0.45; $P < .001$) (Table 2 and Figure, B). Additionally, the most pronounced reduction in the estimated probability of survival was found when the time to WB transfusion was after 14 minutes from 0.961 (95% CI, 0.855-1.067) at 14 minutes to 0.913 (95% CI, 0.806-1.020) at 15 minutes, with a risk difference of 5.7% (95% CI, 3.93%-7.46%) at the following 15-minute time point. For the secondary outcome of survival at 4 hours, for every 1-minute increase in time to WB transfusion, there was an associated increase in risk of mortality (HR, 1.15; 95% CI, 1.07-1.25; $P < .001$) (**Table 3** and eTable 2, eFigure 1, and eFigure 2 in Supplement 1).

Among patients who received an earlier WB transfusion compared with those who received a later WB transfusion at any given time, there was no significant difference in the adjusted odds ratio for overall in-hospital major complications (0.96; 95% CI, 0.58-1.57; $P = .86$). Last, there were no statistically significant differences in total hospital LOS or ICU LOS among patients who received an earlier WB transfusion compared with a later WB transfusion after adjusting for confounders (hospital LOS: incidence rate ratio, 0.98; 95% CI, 0.86-1.12; $P = .74$; ICU LOS: incidence rate ratio, 0.95; 95% CI, 0.81-1.10; $P = .49$) (Table 3 and eTable 3 in Supplement 1).

Discussion

The results from this analysis showed a survival benefit at 24 hours and 30 days associated with WB transfused earlier compared with later for any given time point within the first 24 hours after ED arrival among patients presenting with or at risk of severe hemorrhage in adult civilian trauma centers in the US and Canada. The survival curves showed a difference early within the first hour of ED arrival and the initial WB transfu-

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sion, demonstrating an associated increased risk of mortality for every 1-minute increase in the time to initial WB transfusion during the first 4 hours. Additionally, the findings demonstrated the most prominent inflection point for reduced survival when WB transfusion was given after 14 minutes from ED arrival. The findings from this study suggest that the timely beneficial effect of WB may, in part, be secondary to a prompter delivery of a high-ratio transfusion to mitigate the detriments of TIC.

The momentum for the routine use of WB to facilitate hemostatic resuscitation among trauma centers has been reasonably challenged owing to the uncertainties as to which subset of patients would benefit the most and the lack of definition of when patients should receive WB transfusion as part of MTP. Due to these uncertainties, the ACS TQIP management guidelines for massive transfusion in trauma have yet to adopt WB as part of MTP.[25]

Despite the lack of consensus and data regarding WB transfusion in trauma patients, Cotton et al[26] recognized the potential for WB, assimilating the military's experience and associated improved outcomes with WB into the civilian setting.[27-29] Cotton et al[26] conducted a pilot randomized clinical trial of 107 patients that compared WB plus MTP with MTP alone in severely injured trauma patients requiring large-volume transfusions. The study showed no difference in secondary outcomes of 24-hour or 30-day mortality rates. However, several critical limitations to that trial related to WB availability likely affected the results. The trial was conducted in 2013, prior to the US Food and Drug Administration's and the Association for the Advancement of Blood and Biotherapies' approval of WB in the civilian setting. Patients in the study with group B and AB blood types were excluded given the safety concerns related to ABO compatibility. Furthermore, mandatory patient blood typing created significant delays in time to WB transfusion, hindering the efficiency and, at times, the capability to use WB altogether in patients needing time-sensitive resuscitation. However, the 31st edition of the Association for the Advancement of Blood and Biotherapies standards in 2018 was receptive to using low-titer anti-A and anti-B group O whole blood (LTOWB) in the civilian setting without cross-matching, making WB readily accessible for emergency release.[30] Given the eased restrictions of WB for emergency use, 2 prospective studies by Brill et al[4] and Hazelton et al[5] examined the survival benefit of WB compared with component therapy in bleeding trauma patients. Both studies concluded that there was significantly improved survival among trauma patients who received WB.

More recently, Sperry et al[31] conducted a prospective, multicenter cohort study of 1051 trauma patients at risk for massive transfusion, comparing those who received prehospital or early in-hospital LTOWB with those who received component therapy only. The study showed no difference in the primary outcome of 4-hour mortality and no difference in the secondary outcomes of 24-hour and 28-day mortality. Nonetheless, the authors emphasized that for patients with an elevated probability of mortality, LTOWB was independently associated with a lower risk of mortality starting at 4 hours after ED arrival and through 28 days. The lack of a well-defined cohort of injured patients who should receive WB may explain the absence of clinical benefit in this and other studies with similar outcome findings.[32] Recognizing this constraint, Torres et al[7] sought to explicitly define and evaluate a group of patients who would

Table 1. Overall Cohort Characteristics at ED Arrival

Characteristics	Patients (N = 1394)[a]
Age, median (IQR), y	39 (25-51)
Race	
Asian	18 (1)
Black	410 (29)
White	787 (56)
BMI, median (IQR)	28 (24-32)
Sex	
Female	239 (17)
Male	1155 (83)
ED vital signs, median (IQR)	
Systolic blood pressure, mm Hg	81 (70-90)
Heart rate, /min	120 (104-139)
Shock index	1.5 (1.2-1.7)
Glasgow Coma Scale score[b]	11 (3-15)
Head AIS score	2 (0-3)
Penetrating injury	504 (36)
ISS	
Median (IQR)	27 (17-35)
1-8	72 (5)
9-15	214 (15)
16-24	343 (25)
25-75	765 (55)
Comorbidities	
Diabetes	142 (10)
Hypertension	262 (19)
COPD	96 (7)
Stroke	83 (6)
Chronic kidney disease	72 (5)
ACS trauma center (n = 173)	
Level 1	110 (64)
Level 2	63 (36)
Intervention for hemorrhage control	1216 (87)
Angiography	310 (22)
Time to angiography, median (IQR), min	44 (0-97)
Surgery	906 (65)
Time to surgery, median (IQR), min	65 (0-73)
Time to first MTP transfusion, median (IQR), min	36 (9-37)
Transfusion amount at 4 h, median (IQR), U	
WB	2 (1-2)
pRBCs	5 (3-7)
Plasma	6 (3-7)
Platelets (pooled pack)	1 (0-1)
Cryoprecipitate	1 (0-1)

Abbreviations: ACS, American College of Surgeons; AIS, Abbreviated Injury Scale; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; ED, emergency department; ISS, Injury Severity Score; MTP, massive transfusion protocol; pRBC, packed red blood cell; WB, whole blood.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Scores range from 3 to 15, with higher scores indicating improved responsiveness.

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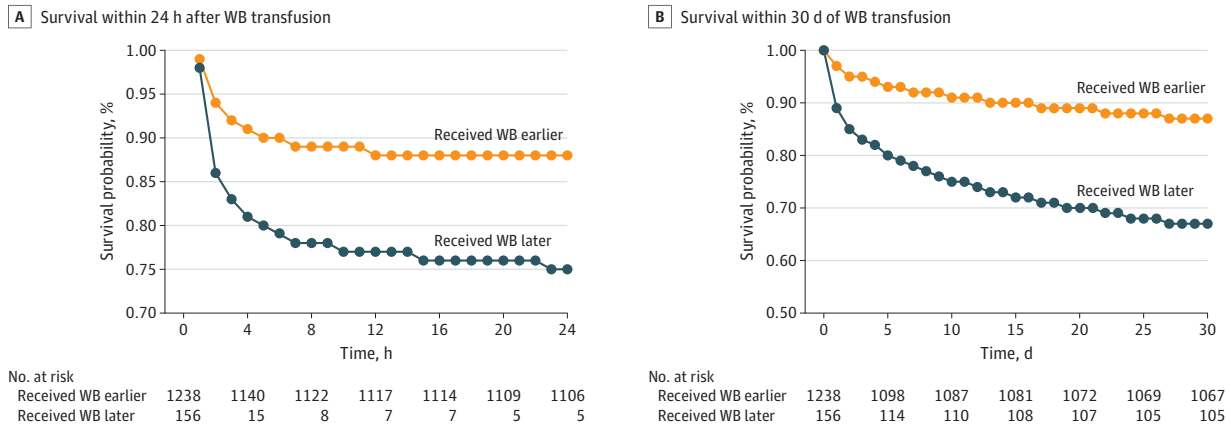
Table 2. Adjusted Parametric Hazard Regression Treatment Effect Estimates

Variable	Mortality at 24 h		Mortality at 30 d	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Time to WB transfusion[a]				
WB later	1 [Reference]	NA	1 [Reference]	NA
WB earlier	0.40 (0.22-0.73)	.003	0.32 (0.22-0.45)	<.001
ISS, per 1-category increase	1.35 (1.05-1.74)	.02	1.50 (1.18-1.90)	.001
Total GCS score, per 1-point increase	0.85 (0.82-0.89)	<.001	0.88 (0.85-0.91)	<.001
Penetrating injury	1.12 (0.74-1.70)	.58	1.13 (0.78-1.65)	.52
Time to bleeding control, per 1-min increase				
Time to angiography	0.86 (0.71-1.04)	.12	0.93 (0.82-1.06)	.27
Time to surgery	1.01 (0.94-1.09)	.74	0.96 (0.90-1.04)	.32
Intervention for bleeding control				
Angiography	1.14 (0.77-1.69)	.52	0.95 (0.65-1.39)	.80
Surgery	0.88 (0.79-0.99)	.03	0.84 (0.74-0.95)	.005
Trauma center				
Level 1	1 [Reference]	NA	1 [Reference]	NA
Level 2	1.50 (1.07-2.11)	.02	1.63 (1.16-2.29)	.005
Time to first MTP transfusion, per 1-min increase	0.74 (0.59-0.94)	.01	0.72 (0.52-0.98)	.04
Age, per 10-y increase	1.32 (1.20-1.45)	<.001	1.39 (1.25-1.55)	<.001
Male	1.47 (1.05-2.06)	.03	1.71 (1.21-2.42)	.03
Systolic blood pressure, per 1-mm Hg increase	0.99 (0.98-0.99)	.01	0.98 (0.97-0.99)	.007
Pulse, per 1-point increase, /min	1.00 (0.99-1.01)	.10	1.01 (1.00-1.02)	.009

Abbreviations: GCS, Glasgow Coma Scale; HR, hazard ratio; ISS, Injury Severity Score; MTP, massive transfusion protocol; NA, not applicable; WB, whole blood.

[a] The counterfactual exposure at each time point.

Figure. Standard Survival Curves of Whole Blood (WB) Transfusion Timing



Estimated survival probability of patients who received WB as an adjunct to the component-based massive transfusion protocol earlier vs later during the first 24 hours after emergency department arrival. Every patient received WB.

likely benefit the most from WB. The study retrospectively analyzed a cohort of 2785 adult trauma patients presenting with severe hemorrhage who had received WB as an adjunct to MTP compared with MTP alone. The results of the study showed that WB plus MTP was associated with a 37% and 47% lower risk of mortality at 24 hours and 30 days, respectively. Similarly, the population in our study was chosen to reflect patients with severe hemorrhage who are at the most significant risk of bleeding-related death. The patients analyzed in our study were profoundly injured, with a median Injury Severity Score of 27 (IQR, 17-35) and an overall 30-day mortality rate of 16%. Interestingly, despite the significantly injured patient population, the 30-day mortality rate was noticeably lower than the 20% to 25% mortality rate reported among similar injured and exsanguinating patients.[3,33-35] However, the lower mortality rate observed in our study could be explained by the fact that all patients in our study received WB as an adjunct to MTP, whereas the prior studies only used traditional component therapy-based MTP without WB. This observation alone is hypothesis generating, showing the potential treatment effect of WB.

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Table 3. Secondary Outcomes

Outcome	All patients (N = 1394)		Patients with severe head injury (n = 405)	
Mortality	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
4 h[a]	1.15 (1.07-1.25)	<.001	3.45 (2.12-5.56)	<.001
24 h[b]	0.40 (0.22-0.73)	.003	0.30 (0.15-0.55)	<.001
30 d[b]	0.32 (0.22-0.45)	<.001	0.31 (0.20-0.46)	<.001
Complications	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Acute kidney injury	0.70 (0.38-1.29)	.26	0.53 (0.23-1.20)	.13
Pulmonary embolism	1.30 (0.49-3.49)	.60	0.55 (0.16-1.89)	.34
Deep vein thrombosis	0.72 (0.39-1.32)	.30	0.92 (0.34-2.54)	.89
ARDS	2.02 (0.60-6.93)	>.99	1.09 (0.24-5.07)	.91
Stroke	NA	NA	NA	NA
Overall	0.96 (0.58-1.57)	.86	0.69 (0.34-1.41)	.31
Length of stay	**IRR (95% CI)**	***P* value**	**IRR (95% CI)**	***P* value**
Hospital	0.98 (0.86-1.12)	.74	1.12 (0.90-1.40)	.30
ICU	0.95 (0.81-1.10)	.49	0.97 (0.75-1.24)	.80

Abbreviations: ARDS, acute respiratory distress syndrome; HR, hazard ratio; ICU, intensive care unit; IRR, incidence rate ratio; NA, not applicable; OR, odds ratio.

[a] Per 1-minute increase to time to first whole blood transfusion.

[b] Whole blood transfusion given earlier compared with later at any time point within the first 24 hours of emergency department arrival.

Underscoring the importance of the effects of timing and prompt blood product delivery, Meyer et al[36] performed a subanalysis of the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial[3] to evaluate the effect of timing of first blood product delivery on patient outcomes. The study found that delays in MTP activation and initial blood product delivery were associated with increased mortality at 24 hours independent of product ratios. Logically, the early and timely administration of WB would confer the same benefits.

A recent study by Hosseinpour et al[37] attempted to examine the association of time to WB transfusion with outcomes among injured patients. The authors conducted a retrospective analysis of adult trauma patients who received at least 1 unit of WB and stratified by time that the first unit of WB was transfused (first 30 minutes, second 30 minutes, and second hour). The study concluded that WB transfusion after 30 minutes was associated with an increased odds of death at 24 hours and in the hospital. Taken together, the present study and the study by Hosseinpour et al[37] suggest that timing is an important variable in survival associated with WB. However, several critical differences exist between the present study and the study of Hosseinpour et al.[37] First, the study by Hosseinpour et al[37] included any patient who received WB without any additional physiological criteria or consideration for the need for MTP. Our study contributes to the narrative of these data, as it specifically evaluated patients with evidence of shock. Additionally, we evaluated patients with severe head injuries. The presence of significant head injury among patients who received WB for severe hemorrhage still demonstrated improved survival compared with MTP alone in prior studies.[4,7] The results from our subgroup analysis of patients with severe head injury demonstrated a statistically significant improvement in time to survival at 4 hours, 24 hours, and 30 days associated with WB given earlier at any time point. This implies that WB should also be considered for severely bleeding trauma patients with a concomitant severe head injury. Second, we performed a survival analysis instead of logistic regression. Logistic regression lacks the element of time involved in estimating an outcome. Therefore, it cannot analyze time-to-event data; rather, the model simply estimates whether or not a binary outcome has occurred. Conversely, survival analysis has the advantage of recognizing outcome events continuously at different time points, considers patients who were censored (discharged or transferred) before the end of the evaluation period, and has greater statistical power to detect a significant treatment effect compared with logistic regression.[38,39] Last, we kept the timing of WB transfusion as a time-dependent continuous variable rather than stratifying groups by time to transfusion. We considered this critical, as dichotomizing a continuous variable would reduce statistical power to detect the association between our variable of interest (time to WB transfusion) and the outcome, increase the risk of a result being false positive, significantly underestimate the degree of variation in outcome between groups, and obscure any nonlinearity in the association between the variable and outcome.[40,41]

Beyond the statistical implications, we considered the clinical ramifications of categorizing a time-sensitive intervention for patients experiencing rapid blood loss, when every passing minute is critical. The use of a continuous model helps clarify the implications of receiving WB at 3 minutes vs 29 minutes. Furthermore, our study addressed outcomes using a counterfactual scenario, comparing patients who received WB with those who had not yet received WB at each time point.

Limitations

This study has several limitations. This retrospective analysis based on a national database examined the association between WB transfusion timing and improved survival. However, it is essential to note that the observed benefits were merely associated with the time to first WB transfusion and should not be interpreted as a direct cause. Since this study was observational and lacked randomization, there was an inherent risk of confounding factors due to clinical indications and other potentially unmeasured biases. Trauma centers using WB as a transfusion approach often store WB in the trauma bay, ensuring swift availability of emergency release transfusion for hemostatic resuscitation. This proximity and immediate ac-

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cess to WB increases the likelihood of patients receiving it shortly after arriving at the ED. However, it is important to consider confounding by indication in this scenario, as the benefits of administering WB early may be overestimated. It is possible that patients who received WB soon after arrival would have fared well regardless, thereby skewing the assessment of its positive effects.

Furthermore, our ability to consider the rate of specific ED procedures that could potentially lead to a delay of the initial WB transfusion in the later recipients was limited. This factor could be an indirect indicator of worse injury severity and, consequently, unfavorable consequences within the later group. Nevertheless, to address this potential bias, we purposefully incorporated a cohort of severely injured patients with a historical 30-day mortality rate surpassing 20%.

Our study was subject to other certain database limitations, including the absence of laboratory data, practitioner-level data, and information on the administration of tranexamic acid. Moreover, TQIP does not provide specific details regarding the type of WB used. These uncaptured variables allow for unmeasured biases.

Our study did not reveal statistically significant differences in major complications among patients who received WB earlier. However, this limitation might be attributed to the insufficient power of our study to identify smaller differences. Nonetheless, these important outcomes impacting patients deserve closer examination in future research.

Finally, prehospital blood product transfusion is not specified in the TQIP data set. The study conducted by Sperry et al[18] revealed a survival advantage for patients with severe hemorrhage who received blood products prior to reaching the hospital. Conversely, a more recent prospective observational study by Sperry et al[31] evaluating prehospital WB for patients with severe hemorrhage found that WB was associated with improved survival at 4 hours and 28 days from ED arrival in patients with at least a 5% mortality risk.

Conclusion

In this retrospective cohort study, early receipt of WB at any time point within the first 24 hours of ED arrival was associated with improved survival in patients presenting with severe hemorrhage. The survival benefit was noted shortly after transfusion. Therefore, WB resuscitation given as soon as possible may provide a survival advantage in actively hemorrhaging patients. Further prospective studies are warranted to complement our results to incorporate these findings into MTPs and further understand best WB transfusion practices.

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Concept and design: Torres, Brahmbhatt, Dechert, Sakran.
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Invited Commentary

Time to First Whole Blood Associated With Survival—First (Whole) Blood?

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Despite significant advances in resuscitation and management over time, mortality from traumatic injury continues to occur early, commonly within hours of arrival to definitive trauma care.[1,2] Literature consistently has demonstrated that treatments associated with improved outcomes are time sensitive, highlighting the prehospital and early emergency department phase of care for such interventions.[3,4]

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Torres et al[5] have again demonstrated a significant survival advantage attributable to whole-blood resuscitation but focused specifically on when it was provided to patients—earlier vs later in the first 4 hours of resuscitation. This retrospective cohort analysis using the American College of Surgeons Trauma Quality Improvement Program data set from 2019 to 2020 allowed for a robust time-focused analysis and further highlights the potential of early whole blood as a resuscitative product of choice.

This study, along with other recent reports that whole-blood resuscitation reduces transfusion requirements in addition to improving mortality, adds to the mounting observational evidence in support of whole blood transfusion in trauma. Observational studies have limitations including the potential for bias and residual confounding. Appropriate char-

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